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## Enantioselective Symmetry Breaking Directed by the Order of Process Steps

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Supporting Information

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**Enantioselective Symmetry Breaking Directed by the Order of Process Steps\*\***

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## Supporting Information

### Unbiased reverse experiments

In a standard reaction vial (10 mL) 8.0 g glass beads and 6.25 g MeCN were added together with 0.15 g 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction vial was placed on a thermostated ultrasonic cleaning bath. After 5 minutes of ultrasonic induced mixing, the reaction vial was removed from the cleaning bath and 0.40 g (*RS*)-**1** was added. A saturated solution was created by frequently manually shaking the flask for 2 hours. Then, the reaction mixture was placed back in the ultrasonic cleaning bath and the solid phase was deracemized under grinding conditions. The enantiomeric excess (*ee*) in the solid phase was followed by taking ca. 0.2 mL slurry samples that were filtered on a P4 glass filter and washed with ca. 0.1 mL MeOH. Subsequently, the solid was completely dissolved in isopropanol and the *ee* was determined using a chiral HPLC (Chiralpak AD-H (250x4.6 mm ID), eluent n-hexane/2-propanol 80/20 v/v%, flow 1mL/min, detection  $\lambda=254$  nm. Retention times (*R*)-**1** 7.9 min, (*S*)-**1** 8.5 min).

### Biased nucleation deracemization experiments

To a standard reaction vial containing a magnetic stirring bar were added 0.01 g (*S*)-Phenyl glycine ((*S*)-**2**) 6.0 g MeCN, 0.3 g (*RS*)-**1** and 0.1 g DBU. The mixture was heated until a clear solution was obtained and gradually cooled down to room temperature under stirring conditions (300 rpm) overnight. The resulting precipitate was filtered and analyzed using the above described HPLC method. A similar experimental procedure was followed for (*R*)-phenyl glycine ((*R*)-**2**).

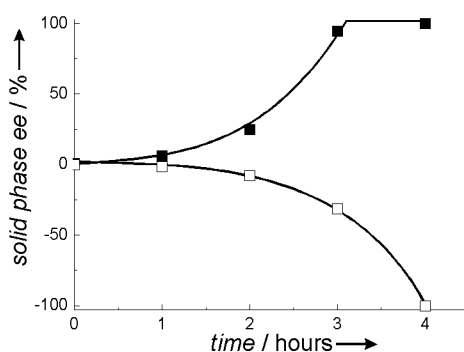
### Biased dissolution directed deracemization experiments

First of all, two solutions need to be prepared (A and B).

A: In a standard reaction vial 0.3 g (*RS*)-**1** is partially dissolved in 6.0 g MeCN and shaken using the thermostated ultrasonic cleaning bath for 1h to establish a saturated solution.

B: In a standard reaction vial is placed ca. 0.0002 g (*S*)-Phenyl glycine with 5.7 g MeCN and mixed for 10 min using the thermostated ultrasonic cleaning bath. Subsequently, the solution was filtered over a 0.2  $\mu\text{m}$  Whatman filter. To this solution was added 0.2 g DBU and 0.35 g (*RS*)-**1**. A saturated solution was created by frequently manually swirling the flask very gently for 2 hours. After this, the clear solution was gently removed using a pipette, leaving the crystals at the bottom of the reaction flask. To the flask were added 8.0 g glass beads and 5.5 g of the solution in flask A. This mixture was placed in the ultrasonic cleaning bath for 10 min. Then 0.2 g DBU was added to the mixture to initiate the solution phase deracemization reaction and the solid phase was deracemized under grinding conditions. The solid phase *ee* was determined using the method described above (Figure SI 1).

A similar procedure was followed for testing the (*R*)-phenyl glycine as an enantioselective dissolution additive.



**Figure SI 1.** The evolution of the *ee* in the solid phase during the deracemization of **1** after dissolution in the presence of enantiopure phenyl glycine **2**. Positive *ee* values are used for the (*S*)-**1**. Closed symbols are for the dissolution in the presence of (*S*)-**2**, open symbols for (*R*)-**2**.